Translating animal research into clinical benefit

Poor methodological standards in animal studies mean that positive results may not translate to the clinical domain

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Most treatments are initially tested on animals for several reasons. Firstly, animal studies provide a degree of environmental and genetic manipulation rarely feasible in humans.[1] Secondly, it may not be necessary to test new treatments on humans if preliminary testing on animals shows that they are not clinically useful. Thirdly, regulatory authorities concerned with public protection require extensive animal testing to screen new treatments for toxicity and to establish safety. Finally, animal studies provide unique insights into the pathophysiology and causes of disease, and often reveal novel targets for directed treatments. Yet in a systematic review reported in this week's *BMJ* Perel and colleagues find that therapeutic efficacy in animals often does not translate to the clinical domain.[2]

The authors conducted meta-analyses of all available animal data for six interventions that showed definitive proof of benefit or harm in humans. For three of the interventions—corticosteroids for brain injury, antifibrinolytics in haemorrhage, and tirilazad for acute ischaemic stroke—they found major discordance between the results of the animal experiments and human trials. Equally concerning, they found consistent methodological flaws throughout the animal data, irrespective of the intervention or disease studied. For example, only eight of the 113 animal studies on thrombolysis for stroke reported a sample size calculation, a fundamental step in helping to ensure an appropriately powered precise estimate of effect. In addition, the use of randomisation, concealed allocation, and blinded outcome assessment—standards that are considered the norm when planning and reporting modern human clinical trials—were inconsistent in the animal studies.

A limitation of the review is that only six interventions for six conditions were analysed; this raises questions about its applicability across the spectrum of experimental medicine. Others have found consistent results, however. In an overview of similar correlative reviews between animal studies and human trials, Pound and colleagues found that the results of only one—thrombolytics for acute ischaemic stroke—showed similar findings for humans and animals.[3] In our systematic review of 76 highly cited (and therefore probably influential) animal studies, we found that only just over a third translated at the level of human randomised trials.[4] Similar results have been reported in cancer research.[5]

Why then are the results of animal studies often not replicated in the clinical domain? Several possible explanations exist. A consistent finding is the presence of methodological biases in animal experimentation; the lack of uniform requirements for reporting animal data has compounded this problem. A series of systematic reviews has shown that the effect size of animal studies is sensitive to the quality of the study and publication bias.[6 7 8] A review of 290 animal experiments presented at emergency medicine meetings found that animal studies that did not use randomisation or blinding were much more likely to report a treatment effect than studies that were randomised or blinded.[9]

A second explanation is that animal models may not adequately mimic human pathophysiology. Test animals are often young, rarely have comorbidities, and are not exposed to the range of competing (and interacting) interventions that humans often receive. The timing, route, and formulation of the intervention may also introduce problems. Most animal experiments have a limited sample size. Animal studies with small sample sizes are more likely to report higher estimates of effect than studies with larger numbers; this distortion usually regresses when all available studies are analysed in aggregate.[10 11] To compound the problem, investigators may select positive animal data but ignore equally valid but negative work when planning clinical trials, a phenomenon known as optimism bias.[12]

What can be done to remedy this situation? Firstly, uniform reporting requirements are needed urgently and would improve the quality of animal research; as in the clinical research world, this would require cooperation between investigators, editors, and funders of basic scientific research. A more immediate solution is to promote rigorous systematic reviews of experimental treatments before clinical trials begin. Many clinical trials would probably not have gone ahead if all the data had been subjected to meta-analysis. Such reviews would also provide robust estimates of effect size and variance for adequately powering randomised trials.

A third solution, which Perel and colleagues call for, is a system for registering animal experiments, analogous to that for clinical trials. This would help to reduce publication bias and provide a more informed view before proceeding to clinical trials. Until such

improvements occur, it seems prudent to be critical and cautious about the applicability of animal data to the clinical domain.

1 Lemon R, Dunnett SB. Surveying the literature from animal experiments. *BMJ* 2005;330:977-8.
2 Perel P, Roberts I, Sena E, Wheble P, Briscoe C, Sandercock P, et al. Comparison of treatment effects between animal experiments and clinical trials: systematic review. *BMJ* 2007 doi: 10.1136/bmj.39048.407928.BE.
3 Pound P, Ebrahim S, Sandercock P, Bracken MB, Roberts I. Where is the evidence that animal research benefits humans? *BMJ* 2004;328:514-7.
4 Hackam DG, Redelmeier DA. Translation of research evidence from animals to humans. *JAMA* 2006;296:1731-2.
5 Corpet DE, Pierre F. How good are rodent models of carcinogenesis in predicting efficacy in humans? A systematic review and meta-analysis of colon chemoprevention in rats, mice and men. *Eur J Cancer* 2005;41:1911-22.
6 Macleod MR, O'Collins T, Horky LL, Howells DW, Donnan GA. Systematic review and meta-analysis of the efficacy of FK506 in experimental stroke. *J Cereb Blood Flow Metab* 2005;25:713-21.
7 Macleod MR, O'Collins T, Howells DW, Donnan GA. Pooling of animal experimental data reveals influence of study design and publication bias. *Stroke* 2004;35:1203-8.
8 O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. *Ann Neurol* 2006;59:467-77.
9 Bebarta V, Luyten D, Heard K. Emergency medicine animal research: does use of randomization and blinding affect the results? *Acad Emerg Med* 2003;10:684-7.
10 Lee DS, Nguyen QT, Lapointe N, Austin PC, Ohlsson A, Tu JV, et al. Meta-analysis of the effects of endothelin receptor blockade on survival in experimental heart failure. *J Card Fail* 2003;9:368-74.
11 Roberts I, Kwan I, Evans P, Haig S. Does animal experimentation inform human health care? Observations from a systematic review of international animal experiments on fluid resuscitation. *BMJ* 2002;324:474-6.
12 Chalmers I, Matthews R. What are the implications of optimism bias in clinical research? *Lancet* 2006;367:449-50.

Exercise and menstrual function

Up to four fifths of women who exercise vigorously may have some form of menstrual dysfunction

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The risks to sportswomen of exercise related menstrual dysfunction and impaired bone health are important and under-recognised. Exercise related menstrual dysfunction may include any abnormality along the continuum of luteal phase deficiency, anovulation, oligomenorrhoea, amenorrhoea, and delayed menarche. Such dysfunction is multifactorial in origin, with a high degree of individual variation, but its main underlying mechanism is hypothalamic inhibition with suppression of gonadotrophin releasing hormone pulsatility (the frequency at which pulses of the hormone are released by the hypothalamus).[1]

This hypothalamic suppression has a variety of causes in sportswomen, including the physical and psychological stress of training and competition, caloric deficiency, low body mass, low body fat,[1 2] inadequate leptin values, and altered peripheral hormone metabolism. Relative hyperandrogenism and genetic influences may also have a role.[1] The consequences can include musculoskeletal injuries (in particular stress fractures), infertility, and the general medical consequences of hypo-oestrogenism.

When menstrual dysfunction (in particular amenorrhoea) occurs in sportswomen in combination with low bone mass and energy deficit, the syndrome is termed the "female athletic triad." This is a complex and poorly understood disorder seen in females who exercise intensively.[2 w1] Athletes in lightweight sports (distance running, gymnastics, lightweight rowing) are at high risk, although the syndrome can arise in relation to any sport. The energy deficit is usually related to eating disorders and is partly influenced by peer pressure. Genetic, neurochemical, and psychodevelopmental factors may also contribute, along with the physical and psychological effects of training and competition. The long term effects tend to be greatest in young girls who start intense exercise before menarche. These girls have an increased chance of delayed menarche, impairment of growth and pubertal progression, subsequent menstrual dysfunction, and suboptimal bone health.[1 4]

Secondary amenorrhoea occurs in up to 44% of women who exercise vigorously, compared with 2-5% of the general population.[1 5 6] Athletes who present with amenorrhoea are at the severe end of the spectrum of exercise related menstrual dysfunction. Subtle menstrual disturbances are more common, occurring in nearly four fifths of very active women. The impact of this on bone mineral density is unclear,[8 9] and there is no evidence that women whose menstrual function recovers develop chronic infertility.

No specific threshold at which exercise leads to menstrual dysfunction has been defined because contributing physiological and psychological factors produce considerable individual variation. However, women who run more than 50 miles each week have a significantly increased incidence of amenorrhoea.[10]

Screening may be useful in women who exercise vigorously. Dietary, medical, and training histories should be taken from any apparently physically fit woman presenting with recurrent or resistant injuries to soft tissue or bone (in particular stress fractures). Women with eating disorders are often reluctant to describe their diet, however. Urinalysis to detect ketonuria will suggest inadequate caloric intake, and thyroid function tests (yielding normal or raised thyroid stimulating hormone and reduced free thyroxine) will indicate a hypometabolic state.

Women who are amenorrhoeic will need the standard investigations. In women with suspected luteal phase deficiency basal body temperature should be monitored, surges in luteinising hormone measured with ovulation predictor kits, multiple samplings of serum progesterone taken, and ideally, endometrial

biopsy carried out. Women with suspected bone loss may need a DEXA (dual energy x ray absorptiometry) scan, preferably including peripheral sites such as the tibia and forearm.[w2]

Management of exercise related menstrual dysfunction aims primarily to restore normal menstrual cycles. Education of patients, coaches, peers, and parents about the risks of excessive exercise in girls and women is of paramount importance. Dietary counselling to ensure a positive energy balance and adequate calcium and vitamin D intake,[w3] and advice on altering the volume and intensity of training programmes and reducing the stressors of competition, may be effective. Supplementation with combined oestrogen and progesterone should help maintain bone mass, although it will not rebuild what has already been lost.[11] Treatment with recombinant leptin may have a role in the future but evidence is preliminary.[12]

1 De Cree C. Sex steroid metabolism and menstrual irregularities in the exercising female. A review. *Sports Med* 1998;25:369-406.
2 Otis CL, Drinkwater B, Johnson M, Loucks A, Wilmore J. American College of Sports Medicine position stand. The female athlete triad. *Med Sci Sports Exerc* 1997;29:i-ix.
3 Laughlin GA, Yen SS. Hypoleptinemia in women athletes: absence of a diurnal rhythm with amenorrhea. *J Clin Endocrinol Metab* 1997;82:318-21.
4 Kanaka-Gantenbein C. The impact of exercise on thyroid hormone metabolism in children and adolescents. *Horm Metab Res* 2005;37:563-5.
5 Loucks AB, Horvath SM. Athletic amenorrhea: a review. *Med Sci Sports Exerc* 1985;17:56-72.
6 Petterson F, Fires H, Nillius SJ. Epidemiology of secondary amenorrhea: incidence and prevalence rates. *Am J Obstet Gynecol* 1973;117:80-6.
7 De Souza MJ. Menstrual disturbances in athletes: a focus on luteal phase defects. *Med Sci Sports Exerc* 2003;35:1553-63.
8 De Souza MJ, Van Heest J, Demers LM, Lasley BL. Luteal phase deficiency in recreational runners: evidence for a hypometabolic state. *J Clin Endocrinol Metab* 2003;88:337-46.
9 De Souza MJ, Miller BE, Sequenzia LC, Luciano AA, Ulreich S, Stier S, et al. Bone health is not affected by luteal phase abnormalities and decreased ovarian progesterone production in female runners. *J Clin Endocrinol Metab* 1997;82:2867-76.
10 Cumming DC, Rebar DW. Exercise and reproductive function in women: a review. *Am J Ind Med* 1983;4:113.
11 Hergenroeder AC. Bone mineralization, hypothalamic amenorrhea, and sex steroid therapy in female adolescents and young adults. *J Pediatr* 1995;126:683-9.
12 Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* 2004;351:987-97.
Extra references w1-w3 are on bmj.com

Clinical trials in emergency situations

New guidance allows patients to be enrolled without prior consent

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On 12 December 2006 an amendment of the UK's Medicines for Human Use (Clinical Trials) Regulations 2004 came into force.[1] The amendment allows unconscious patients in emergency situations to be enrolled in clinical trials without prior consent provided that this has been approved by the appropriate ethics committee. The amendment has been anxiously awaited by emergency care researchers since these regulations first changed the legal basis for consent for research on medicinal products in the United Kingdom in May 2004.[2]

Researchers have always been concerned about the effects the regulations might have on clinical trials in emergency situations in patients with impaired consciousness, such as those with head injury, major trauma, or cardiac arrest. The regulations imposed the need for prior consent from a personal or professional legal representative before a patient could be recruited into a clinical trial. The regulations only applied to trials of drugs. Non-medicinal trials and trials of clinical care continued to be governed by common law.[3]

The change in consent procedures was not the only threat to the conduct of clinical trials in emergency care. The increased bureaucracy, reporting, and costs of clinical trials that followed the implementation in 2004 of the European Clinical Trials Directive led to a sharp decline in the initiation of clinical trials and in participant recruitment throughout Europe.[4]

Many important clinical trials such as the TROICA (thrombolysis using tenecteplase (Metalyse) in cardiac arrest) trial foundered because of the new laws.[5] As well as an approved consent procedure, participating National Health Service trusts had to have local procedures, guidance, and training in place to ensure compliance with the regulations. A year after the introduction of regulations, most NHS research and development departments still had no systems in place that would allow emergency care trials in patients with impaired mental capacity.[6]

The CRASH-2 (clinical randomisation of an antifibrinolytic in significant haemorrhage) trial (www.crash2.lshtm.ac.uk) developed a consent protocol in line with the 2004 regulation, which was approved by the UK Medicines and Healthcare Products Regulatory Agency and multicentre research ethics committee and has now recruited more than 3500 patients. However, UK hospital trusts have been slow to implement effective procedures for professional legal representatives for unconscious patients in emergency situations.

The first CRASH trial included patients with severe head injuries, who were unable to give informed consent. It was conducted before implementation of the legislation, and the multicentre research ethics committee gave approval for the trial to be conducted using a "consent waiver." With the approval of the ethics committee, the attending doctor took responsibility for enrolling patients into the trial. Patients and relatives were informed about the trial as soon as possible, and written information on the trial was provided. Of the 10 008 patients randomised, only one patient had to be withdrawn from the trial (at the request of a relative).[7]

Efforts are being made in the UK to redesign the environment in which clinical research is conducted.

This has resulted in the formation of organisations such as the UK Clinical Research Collaboration (www.ukcrc.org). However, in the two years since implementation of the regulations, recruitment into clinical trials in unconscious patients in emergency situations has been slow in the UK.[8] The evidence base for trauma care was already seriously lacking,[9] and the regulations did not help. Unconscious patients in emergency situations should have the right to benefit from medical research, but the 2004 regulations put this right in jeopardy.

The amendment to the clinical trials regulations will be welcomed by emergency doctors. NHS research and development departments urgently need to develop guidance on how to implement this amendment. In the meantime, emergency doctors can be reassured that the new guidance allows patients to be enrolled without prior written consent if approved by the ethics committee, and that clinical trials once again have the potential to provide the evidence needed to improve emergency care.

1 *Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006.* Statutory Instrument 2006 No 2984. www.opsi.gov.uk/si/si2006/20062984.htm.
2 *Medicines for Human Use (Clinical Trials) Regulations 2004.* Statutory Instrument 2006 No 1031. www.opsi.gov.uk/si/si2004/20041031.htm.
3 Department of Health. Reference guide to consent for examination or treatment. London: DOH, 2001. www.dh.gov.uk/assetRoot/04/01/90/79/04019079.pdf.
4 Hemminki A, Kellokumpu-Lehtinen P. Harmful impact of EU clinical trials directive. *BMJ* 2006;332:501-2.
5 Lord Warner. *House of Lords official report* (*Hansard*). Jan 18 2005: col WS25. www.publications.parliament.uk/pa/ld199900/ldhansrd/pdvn/lds05/text/50118-53.htm.
6 Coats TJ, Ng G, Shakur H. Consent in emergency research. *Emerg Med J* 2006;23:489-90.
7 MRC CRASH Collaborators. Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;364:1321-8.
8 Lemaire F. The inability to consent in critical care research: emergency or impairment of cognitive function. *Intensive Care Med* 2006;32:1930-2.
9 Roberts I, Shakur H, Edwards P, Yates D, Sandercock P. Trauma care research and the war on uncertainty. *BMJ* 2005;331:1094-6.

Pregnancy in women with a history of breast cancer

The effect of pregnancy on survival and the best time to conceive are uncertain, so consideration of individual priorities is essential

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Young women diagnosed with breast cancer before completing their families face difficult decisions about future childbearing. Effective treatment tends to reduce fertility, and uncertainties remain regarding the effect of future pregnancy on survival. For women who decide that they do want to become pregnant, the optimal timing of conception is not known.

A population based study by Ives and colleagues in this week's *BMJ* assesses the effect of becoming pregnant on survival after breast cancer.[1] The study used the Western Australian data linkage system to identify 123 women aged 15-44 who became pregnant after being diagnosed with breast cancer. During a median of 10.7 years of follow-up, 39% experienced recurrent breast cancer and 15% died.[1]

The study shows that pregnancy is uncommon after breast cancer; only 4.8% of women aged 15-44 diagnosed with breast cancer became pregnant during the study period and 2.6% had a live birth.[1] The study adds to the limited body of evidence showing that women with breast cancer who become pregnant or have a live birth seem to have comparable or better survival than those who do not.[1 2 3] This evidence is difficult to interpret; women who become pregnant after breast cancer are a highly selected group, and they differ from those who do not become pregnant in ways that affect future survival, including prognostic factors.[4] Women with a worse prognosis are also more likely to receive chemotherapy, which reduces fertility. Furthermore, for reasons that are unclear, women who are pregnant at the time of diagnosis or have given birth during the five years before diagnosis have lower survival rates than other women.[5 6] Such women might be less likely to conceive after diagnosis because they already have children.

Because the relative risk of death after diagnosis can differ more than 30-fold between extreme categories of prognostic variables,[7] even a small amount of residual confounding between prognosis and the decision to get pregnant could generate a spurious protective effect. Many studies adjust for basic prognostic factors, such as tumour size and disease stage. However, it is not possible to account fully for all factors that might influence both survival and whether women get pregnant after breast cancer—including tumour grade, number of positive lymph nodes, treatment, and reproductive history.[1-3] Therefore, we cannot reliably assess the effect that pregnancy after breast cancer has on survival.

Nor can we exclude an adverse effect of pregnancy after breast cancer on survival. Consider this example; observational studies show consistently improved disease-free survival and overall survival in women with breast cancer who use hormonal therapy for the menopause after diagnosis, compared with women who do not (summary relative risk of recurrence 0.64, 95% confidence interval 0.50 to 0.82).[8] The apparent advantage in survival persists after adjustment for disease stage.[9] However, randomised controlled trials show that hormonal therapy for the menopause significantly increases the recurrence of breast cancer (3.41, 1.59 to 7.33).[8] For obvious reasons, randomised data on the effect of pregnancy after breast cancer on survival are not available.

Given these uncertainties and the small number of events in the studies of pregnancy after breast cancer (19 deaths among exposed women in the current study[1]),

insufficient reliable data are available to reach any firm conclusions about how the timing of conception affects survival. It is therefore difficult to see how we will ever be able to answer this question. We need to acknowledge and communicate this uncertainty, and incorporate it into the clinical decision making process.

Large scale randomised trials show that adjuvant radiotherapy, chemotherapy, and, for women with oestrogen receptor positive disease, tamoxifen (and other endocrine therapies) have independent beneficial effects on survival after breast cancer.[10 11] Because of potential teratogenic effects, pregnancy should be avoided during adjuvant treatment. Whereas radiotherapy and chemotherapy are completed within months of surgery, tamoxifen and other endocrine therapies are usually recommended for more than two years. Women with oestrogen receptor positive disease would therefore need to consider the effects of deferring or curtailing the use of tamoxifen if they wanted to conceive during this time.

The rule of thumb recommending at least two years between the diagnosis of breast cancer and conception is an attempt to balance a range of competing considerations, in the face of uncertainty. However, the rule may not be appropriate for all women and should be used judiciously.

What are the implications of the current evidence for women facing decisions about pregnancy after breast cancer and health professionals supporting them? Health professionals can inform women about the risks, benefits, and uncertainties, yet ultimately these decisions will reflect what the women themselves, and those close to them, consider most important. For women who wish to become pregnant after having breast cancer, the ideal timing of conception is unclear, but individual circumstances, such as prognosis and the most appropriate treatment after surgery, need to be considered.

Survival after breast cancer has improved greatly; average survival at five, 10, and 15 years after breast cancer is currently 82%, 73%, and 68%, respectively, in women aged 15-49 in England and Wales.[12] For women with early stage disease, survival is better. Although decisions about pregnancy after a diagnosis of breast cancer raise difficult issues, they are testament to the growing success of treatment and the lives many women are now able to live.

1 Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: population based study. *BMJ* 2007 doi: 10.1136/bmj.39035.667176.55.
2 Mueller B, Simon MS, Deapen D, Kamineni A, Malone KE, Daling JR. Childbearing and survival after breast carcinoma in young women. *Cancer* 2003;98:1131-40.
3 Kroman N, Jensen M, Melbye M, Wohlfahrt J, Mouridsen H. Should women be advised against pregnancy after breast-cancer treatment? *Lancet* 1997;350:319-22.
4 Blakely LJ, Buzdarm AU, Lozada JA, Shullaih SA, Hoy E, Smith TL, et al. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. *Cancer* 2004;100:465-9.
5 Reeves G, Patterson J, Vessey M, Yeates D, Jones L. Hormonal and other factors in relation to survival from breast cancer. *Int J Cancer* 2000;89:293-9.
6 Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Reproductive history and mortality after breast cancer diagnosis. *Obstet Gynecol* 2004;104:146-54.
7 National Cancer Institute. Surveillance Epidemiology and End Results (SEER) Program. *SEER fast stats; breast cancer survival and stage. SEER*Stat database: SEER public-use data 1973-2003*. http://seer.cancer.gov/faststats/sites.php?site=Breast+Cancer&stat=Survival.
8 Col NF, Kim JA, Chlebowski RT. **Menopausal hormone therapy after** breast cancer: a meta-analysis and critical appraisal of the evidence. *Breast Cancer Res* 2005;7:R535-40.
9 O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001;93:754-62.
10 Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-717.
11 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000;355:1757-70.
12 Office for National Statistics. *Long-term breast cancer survival, England and Wales, up to 2003*. www.statistics.gov.uk/StatBase/ssdataset.asp?vlnk=9132&Pos=&ColRank=1&Rank=272.

Mechanical circulatory support in the UK

It is time to do a trial of left ventricular assist devices for lifetime use

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In June the National Institute for Health and Clinical Excellence (NICE) published welcome but bewildering guidelines for short term circulatory support with left ventricular assist devices (LVADs) as a bridge to cardiac transplantation or recovery.[1] Welcome because the guidelines will support funding of these devices but bewildering because few, if any, guidelines for use were actually provided. The limited evidence was derived from the USA and Europe, where LVADs have been used for 20 years, and the guidelines are silent on a third potential use for these devices—their longer term use as a lifetime treatment.

First generation LVADs were designed to replace the failing left ventricle by providing stroke volume and pulsatile blood flow. Blood is taken from the ventricle and pumped in a pulsatile manner into the aorta at a rate of 4-10 litres per minute. These devices provide symptomatic relief, reverse multiorgan dysfunction, and reduce the cytokine and humoral responses to heart failure.[2] Transplant survival is improved following the use of a device.[3] Resting the heart and increasing coronary flow with an LVAD has marked effects on the diseased myocardium. Reduced wall tension and stroke work contribute by decreasing myocyte hypertrophy, apoptosis, myocytolysis, and fibrosis.[4] Myocyte genetic expression and metabolism change towards normal. As a result LVADs can occasionally be removed after function improves in the native heart (bridge to recovery).[5] This occurs more

often with reversible disease such as myocarditis or intoxication.

Currently a transplant is the only operation recognised by NICE for chronic heart failure and is the sole option in congenitally malformed hearts.[6] Survival after a heart transplant is currently over 80% at one year and 50% at 10 years.[7] But in the UK around 150 donor hearts a year are shared among 15 000 patients aged under 65 with stage D chronic heart failure. LVADs are rarely used as a bridge to transplantation. In the EVAD (evaluation of the ventricular assist device programme in the UK) study 70 LVADs were implanted over 32 months.[8] Thirty patients died before transplantation; 32 completed the treatment plan, by later undergoing a transplant; and four recovered without a transplant. The others remain on LVAD support. Overall 12 month survival was 52%. The mean cost of the LVAD implant alone was £63 830 (€97 290; $126 060).[8] Ongoing costs were not provided but many of the patients remained in hospital pending transplantation.

Rather than provide a bridge to transplantation, LVADs may prove more economically viable for lifetime support in patients not eligible for transplantation. Chronic heart failure generates enormous costs through hospital admissions and the use of pacemakers, implantable defibrillators, and drugs. Yet the impact on symptoms and life expectancy of these interventions is modest. The treatment of renal disease sets the precedent. Haemodialysis, with a 60% two year survival, is offered irrespective of age or eligibility for transplantation at a cost of £34 000 per year.[9]

Lifetime use of LVAD has an evidence base in the REMATCH trial (randomised evaluation of mechanical assistance for the treatment of congestive heart failure).[10] Patients with New York Heart Association class IV heart failure who were not candidates for transplantation were randomly assigned to a pulsatile first generation LVAD or continuing medical treatment. At enrolment 68% required intravenous inotropes; the remainder had a peak myocardial oxygen consumption of 9.18 ml/kg/min, highly predictive of early mortality. Median survival in those assigned to the LVAD group was 409 days versus 150 days for controls.[8] The 75% annual mortality for controls exceeded that for AIDS and many cancers. The LVAD provided a 48% reduction in mortality during follow up and 27% reduction at one year. With improved selection of patients an initial 21% two year survival improved to 43% later in the trial. The University of Utah now achieves 85% one year and 65% two year survival, similar to that achieved by haemodialysis in patients with renal disease.[11]

With improved technology, the strategic boundaries between LVAD use for bridge to transplantation, bridge to recovery, and lifetime use no longer exist. The LVAD sustains life while the patient's response determines the clinical course. For instance patients not eligible for a transplant may be rescued with a temporary LAVD and then be switched to lifetime treatment. In future LVADs may also provide the platform for myocardial regeneration by neoangiogenesis or gene or stem cell therapy.

Last July one of us (SW) reported the six year survival in the first patient to receive a miniaturised axial flow pump for lifetime use.[12] The Jarvik 2000 LVAD was tested in laboratory programmes in Houston and Oxford. The 61 year old English patient had idiopathic dilated cardiomyopathy with biventricular failure. He was breathless at rest with pitting oedema to the thighs, ulcerated legs, and ascites. Left ventricular ejection fraction was less than 10%. He was rejected for transplantation because of renal impairment and subsequently declined the procedure. Six years later he has an active life and is in New York Heart Association class II. Pump output is 5.5 l/min against a mean blood pressure of 70-80 mm Hg and usually a pulse pressure of 10-15 mm Hg. Less than 5% of follow-up was spent in hospital. The total cost over the six years has been £115 000. This LVAD has had 100% mechanical reliability in the first 150 implants, and lower complication rates than pulsatile pumps.

A clinical trial of lifetime therapy is now indicated. There are no ethical dilemmas: the technology is proved and the patients have short wretched lives. Moreover, there are questions of equity: is it reasonable to treat end stage renal disease but not heart failure at a similar cost? Should people with potentially recoverable hearts (with idiopathic dilated cardiomyopathy or myocarditis) be directed towards transplantation or offered an LVAD first? These issues should be addressed before this technology is absorbed into the health service without proper assessment. Clinical trials rather than observational studies are essential, though modifications of the classic controlled design may be necessary to study patients whose stage D symptoms have already shown the failure of medical treatment. The NHS is almost the perfect system within which to organise these trials.

1 The National Institute for Health and Clinical Excellence. *Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery*. London: NICE, 2006.
2 Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. *N Engl J Med* 1998;339:1522-33.
3 Frazier OH, Rose AN, McCarthy PM, Burton NA, Tector A, Levin H, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. *Ann Surg* 1995;222:327-8.
4 Zhang J, Narula J. Molecular biology of myocardial recovery. *Surg Clin N Am* 2004;84:223-42.
5 Hetzer R, Muller J, Weng Y, Wallukat G, Spiegelsberger S, Loebe M, et al. Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. *Ann Thorac Surg* 1999;68:742-9.
6 National Institute for Clinical Excellence. *The management of chronic heart failure in primary and second care*. London: NICE, 2003.
7 Deng MC. Orthotopic heart transplantation: highlights and limitations. *Surg Clin North Am* 2004;84:243-5.
8 Sharples LD, Buxton MJ, Caine N. Evaluation of the ventricular assist device programme in the United Kingdom. *J Heart Lung Transplant* 2006;25(suppl 1):80-1.
9 Lee H, Mans B, Taub K, Ghali WA, Dean S, Johnson D, et al. Cost of analysis of ongoing care of patients with end stage renal disease: the impact dialysis modality and dialysis access. *Am J Kidney Dis* 2002;40:611-22.
10 Rose EA, Gelijns AL, Moskowitz AL, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long term use of left ventricular assist device for end stage heart failure. *N Engl J Med* 2001;345:435-43.
11 Park SJ, Tector A, Piccioni W, Raines E, Gelijns A, Moskowitz A, et al. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg* 2005;129:9-17.
12 Westaby S, Frazier OH, Banning A. Six years of continuous circulatory support. *N Engl J Med* 2006;355:325-7.